

UNIVERSITE DE GENEVE
Département de médecine
Cardiologie

FACULTE DE MEDECINE
Professeur P. W. DUCHOSAL
Monsieur Pierre MORET, professeur-assistant

Pulmonary function tests in patients with cancer of the lung

THESE

présentée à la Faculté de médecine de l'Université de Genève
pour obtenir le grade de docteur en médecine

par

Ricardo G. UNDA FREIRE

de

OTAVALO (Imbabura) ECUADOR (Amérique du Sud)

Thèse N° 3361

GENEVE
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La Faculté de médecine, sur le préavis du professeur P.W. Duchosal, autorise l'impression de la présente thèse, sans prétendre par là émettre d'opinion sur les propositions qui y sont énoncées.

Genève, le 25 juillet 1973

Le doyen:
William Geisendorf

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To my parents:

*Juan Gabriel and Laura Inés, Manuel García Matos and Carmen Alonso
Edward Kirchner and Louise*

To my wife:

Celia M. and my son Alejandro G.

C O N T E N T S

INTRODUCTION	1
MATERIALS AND METHODS	2
A. Selection of cases	2
B. Laboratory methods and description	4
C. Statistical Analysis	5
RESULTS	7
<u>PULMONARY FUNCTIONS IN NORMALS</u>	7
- LUNG VOLUMES	7
- LUNG MECHANICS	7
- VENTILATION	7
- DISTRIBUTION AND DIFFUSION TESTS	7
- REGRESSION EQUATIONS	7
<u>PULMONARY FUNCTIONS IN CANCEROUS PATIENTS COMPARED WITH A GROUP OF CHRONIC BRONCHITICS</u>	9
- LUNG VOLUMES	12
- VENTILATION	12
- LUNG MECHANICS	12
- DISTRIBUTION AND DIFFUSION TESTS	16
DISCUSSION	19
CONCLUSIONS	24
BIBLIOGRAPHY	25



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INTRODUCTION

The study of pulmonary functions in patients with cancer of the lung have called the attention of many investigators. The results are still controversial and this may be partly due to the techniques used and to the importance one may ascribe to certain of the pulmonary function tests. The clinical state of the diseased patients, the extent of his lesions and the degree of impingement upon his general physical condition may also play a role, as well as the nature of the lung tumor. Some authors report obstructive syndromes in cancerous patients whereas others stress restrictive patterns. Most report a mixed type syndrome. Some of them insist upon the troubles of diffusion.

The pulmonary function tests are a useful measure of the nature and the extent of lung disease. Most of all, it gives a very valuable evaluation of the operability risks and in certain cases it is of great usefulness in assessing a long term prognosis in lung resected patients.

Those who have experience of the pulmonary function tests are often surprised to find functional troubles far more important than those suspected by clinical examination or by the radiologic image in patients with lung cancer. The evidence of pulmonary dysfunction may only appear upon testing complete pulmonary performance, showing thus that they may be deranged probably due to interstitial lesions or lymphatic lesions which could be far more pronounced than expected.

It has seemed useful for us to reconsider the pulmonary functions of a group of cancerous patients which presented a fairly well localised lesion of the lung relatively well delimited which were in principle operable. This helped to determine the importance and to precise the character of the functional disturbance. Furthermore the reevaluation of pulmonary function is essential in estimating its usefulness as an indication or contraindication for surgery in these patients. It is currently used in guiding anesthetists in chest surgery. To achieve this we have reviewed the pulmonary functions of patients with lung cancer and compared them with a group of normal subjects. In order to better define the functional disturbances secondary to lung cancer we have also compared them with a group of patients with chronic bronchitis.

MATERIALS AND METHODS

A. Selection of cases

From July 1969 until July 1970, a sample group of 1000 patients were taken from the files of the Pulmonary Functions Laboratory. This laboratory receives more or less 900 to 1000 patients per year from the 2000 beds of all services of the Hospital Cantonal which takes care of acute cases from the 350 000 inhabitants of Geneva. These files were transformed into machine-readable data set for computer analysis by the CDC 3800 computer of the CCI (Centre Cantonal d'Informatique) of the University of Geneva. Given that this group of patients does not differ from one year to another it is safe to assume that the 1000 cases drawn from such a period of time are reasonably representative of all the files.

Since the number of females were too small for statistical analysis only male subjects aged from 43 to 74 years old have been kept for our study. The chosen age range is essentially due to the fact that the large majority of patients with cancer of the lung are men within this age group.

Three groups of subjects are considered in this study: normal men, patients with lung cancer and patients with chronic bronchitis. They were selected by computer analysis from the whole sample group. This analysis yielded the following results:

- 104 normal men, mean age: 57.6 ± 8.2 years old.
- 144 men with lung cancer, mean age: 62.0 ± 6.7 years old.
- 172 men with chronic bronchitis, mean age: 61.3 ± 7.8 years old.

The remaining 580 cases were mainly patients with pulmonary silicosis, pulmonary tuberculosis, bronchial asthma and cardiac diseases.

All the cases which did not present any signs or clinical history of respiratory or cardiovascular impairment were considered to be normal. Most of these subjects were sent to the laboratory for respiratory assessment for insurance controls, yearly check-ups, or the preoperative evaluation of pulmonary functions before a surgical intervention other than pulmonary. A great number of normals were smokers (76.9%). Some of them complained at the time pulmonary function determination of slight dyspnoea, coughing and expectoration probably due to smoking. See table I.

Among patients with lung cancer, 93.2% were smokers. 25% did not present any dyspnoea symptoms. 87.5% complained of coughing. 67.4% presented expectorations. From the 144 cancerous patients, 105 were examined within one month after their beginning symptomatology. 21 cases came between the 2nd and the 12th month after the onset of symptoms. All patients with lung

TABLE I
COMPARATIVE TABLE OF CLINICAL SIGNS AND SYMPTOMS
ACCOMPANYING ALL THREE GROUPS OF PATIENTS

	<u>NORMALS</u>		<u>LUNG CANCER</u>		<u>CHRONIC BRONCHITIS</u>	
	<u>Number of cases</u>	<u>Per cent</u>	<u>Number of cases</u>	<u>Per cent</u>	<u>Number of cases</u>	<u>Per cent</u>
<u>SMOKING HABITS</u>						
1. No smokers	20	19.2 %	9	6.3 %	13	7.6 %
2. Smok. pipe or cigars	6	5.8 %	5	3.5 %	11	6.4 %
3. Cigaret. smokers	--	--	--	--	--	--
3.1 From 1 to 10 cig/day	12	11.5 %	16	11.1 %	29	16.9 %
3.2 From 11 to 20 cig/day	23	22.1 %	43	29.9 %	38	22.1 %
3.3 More than 21 cig/day	24	23.1 %	44	30.6 %	40	23.3 %
4. Had smoked (stop since more than 3 mo.)	15	14.4 %	26	18.1 %	33	19.2 %
TOTAL OF CIGARET SMOKERS	59	56.7 %	103	71.6 %	107	62.3 %
TOTAL OF ACTUAL SMOKERS	65	62.5 %	108	75.1 %	118	68.7 %
TOTAL OF ALL SMOKERS	80	76.9 %	134	93.2 %	151	87.9 %
QUESTION NOT ANSWERED	4	3.8 %	1	0.7 %	8	4.7 %
<u>DYSPNEA</u>						
1. None, neither at rest nor upon effort	59	56.7 %	36	25.0 %	9	5.2 %
2. Dyspnea upon exertion	--	--	--	--	--	--
2.1 Slight (after 4 flights of stairs)	28	26.9 %	52	36.1 %	50	29.1 %
2.2 Moderate (after 2-3 fl. stairs) 11	10	9.6 %	41	28.5 %	70	40.7 %
2.3 Moderate (after 1-2 fl. of stairs) 1	--	--	12	8.3 %	35	20.3 %
2.4 Important (some steps, some walking) 1	--	--	--	--	3	1.7 %
3. Dyspnea upon rest	1	1.0 %	--	--	--	--
QUESTION NOT ANSWERED AT ALL	6	5.8 %	3	2.1 %	5	2.9 %
<u>COUGH</u>						
None	66	63.5 %	17	11.8 %	13	7.6 %
Slight to moderate	31	29.8 %	93	64.6 %	109	63.4 %
Important	1	1.0 %	33	22.9 %	49	28.5 %
Question not answered	6	5.8 %	1	0.7 %	1	0.6 %
<u>EXPECTORATIONS</u>						
None	77	74.0 %	44	30.6 %	30	17.4 %
Slight	19	18.3 %	75	52.1 %	97	56.4 %
Moderate	--	--	20	13.9 %	35	20.3 %
Abundant	--	--	2	1.4 %	4	2.3 %
Question not answered	8	7.7 %	3	2.1 %	6	3.5 %
TOTAL OF PATIENTS (MEN ONLY)	104	100.0 %	144	100.0 %	172	100.0 %

Notice: The percentage is calculated from the total number of patients of every group.

cancer were operable after having previously excluded any other clinical contraindication for surgery. The large majority had a fairly well localised lesion and neither metastasis nor important atelectasis were visible on X-rays. In 51% of these patients the lung tumor was localised at the right side and 49% at the left side. 24 patients with lung cancer (16.7% of cancerous group) had a secondary diagnosis added to the first one, namely: 19 patients or (13.2%) had chronic bronchitis. 1 case had specific fibrosis (0.7%). In 3 cases there were found tuberculosis (2.1%). One case was found to have aortic insufficiency (0.7%).

Among the 172 men with chronic bronchitis 87.9% were smokers, this number is slightly superior to that of normal smokers and likewise inferior to that of cancerous smoking patients. The large majority of patients with chronic bronchitis complained of dyspnoea coughing and expectorations. All of these patients had their pulmonary functions measured several months or years after the onset of disease; we have not tried to subdivide their time of appearing symptoms into recent or ancient. At the time of the pulmonary function tests none of these patients had right-sided congestive heart failure. 20 chronic bronchitis patients had a secondary diagnosis; 12 also had asthma (7.0%). And 6 cases had tuberculosis (3.5%).

B. Description of Laboratory methods

All three groups of subjects considered in this paper -normals, patients with lung cancer and patients with chronic bronchitis- had a complete pulmonary function test including:

I. PULMONARY VOLUMES: The static volumes were measured by closed circuit techniques according to classical methods with the PULMOTEST GODART a two bells spirometer apparatus. The functional residual capacity (FRC) and its reciprocal residual volume (RV), was determined by the helium distribution dilution method (7, 22). The PULMOANALYSOR GODART was used as helium analyser whereas the dilution curve was continuously recorded by the MULTICHANNEL RECORDER GODART apparatus. Total lung capacity (TLC) was obtained by adding the vital capacity to the residual volume. The ratio RV/TLC was calculated from the latter values (20).

II. VENTILATORY MECHANICS: Only the one second forced expiratory volume (Tiffeneau or VEMS*) was measured (FEV_1). The maximal voluntary ventilation (MVV) was obtained according to three (15 seconds) successive measurements (10). The ratio FEV_1/VC was also calculated (21). The diminution of the respiratory ventilation (DRV) was obtained by dividing the measured MVV/ predicted MVV x 100, (23).

*) VEMS: Volume expiratoire maximum seconde means one second forced expiratory volume in French.

III. VENTILATION: The minute ventilation ($\dot{V}$) was calculated from a three minutes spirographic recording of tidal volume, during which the oxygen consumption ($\dot{V}O_2$) was also obtained. The respiratory equivalent (EQ) is calculated from the ratio $(\dot{V}/\dot{V}O_2)$, (10).

IV. DISTRIBUTION AND DIFFUSION TESTS: Estimation of the distribution of gases was made by calculating the helium mixing time during the functional residual capacity determination.

The spirometric curve on MVV was also analysed for air trapping or the Creneaux of Anthony. The amplitude of these parameters was recorded as follows: creneaux of slight amplitude were coded for perforated cards for computer analysis as 0-1; creneaux of moderate amplitude were coded: 2. Creneaux of greater amplitude were coded: 3. Evidently these ciphers gave fractional numbers when averaged.

The carbon monoxide diffusing capacity (DL_{CO}), (steady state methods) (6, 8, 13, 29) is measured according to classical methods in bag and box system during 2 minutes (closed circuit technique). A GODART CO-ANALYSOR and DIFFUSION APPARATUS was used.

As only occasional arterial blood gas analyses were performed they are not considered in this study.

All pulmonary function tests were carried out at rest with the patient in a sitting position. All values are given in ATPS units (athmospheric temperature and pressure saturated with water vapor). The altitude of Geneva is 375 m. (1226.5 feet) above sea level. Barometric pressure changes from 718 mm Hg to 745 mm Hg the year round.

C. Description of Statistical Analysis

The values from the files were converted into machine-readable data set by means of perforated cards and statistically analysed by the computer. The main program used was STATIS (11) which yielded contingency or cross classification tables. Mean values and standard deviation were calculated by the STATIS and by BMD 02D program from UCLA (71). Linear regression plots were made by computer program REGLIS (12 b). Student's t-tests and p values were done to compare mean values.

All regression lines shown in coming figures are based on the working hypothesis that they can fit a linear regression. The certainty of this hypothesis has not been tested because of inherent errors which may lead to misinterpretation the straightness of the lines i.e.: age, from 43 to 74 years old, as well as height and weight are given as a mean for the group. It is true however, that from these regression equations the actual regression curve can be obtained (that may or may not be a straight line). Another

point in interpreting these lines correctly must be done by noticing the large dispersion values that are situated beyond the envelopes of their pertaining confidence intervals. This is natural because we do not measure one particular individual at different ages or heights of his entire lifespan, and furthermore knowing that individuals vary extremely from one to another. Our "a priori" assumption, considering all mentioned sources of error, that all values can be fitted into a linear regression rests, after all, valid. Nevertheless care must be exerted especially when there is no evident relationship between a given variable and the parameters with which it is compared.

The envelopes of regression lines represent the confidence intervals for an ordinate (fitted value) to the true regression line within 95% probabilities.

RESULTS

PULMONARY FUNCTIONS IN NORMAL MEN

In order to establish normal values and to compare them with those obtained in two groups of patients, namely those having lung cancer or chronic bronchitis considered in this paper the results obtained from the 104 normal men aged from 43 to 74 years old are reported. See table II. The mean age for this group is: 57.6 ± 8.2 ; mean height is 169.9 ± 6.7 cms. (or 67.9 ± 2.7 inches); mean weight is 72.1 ± 11.3 kg. (or 158.6 ± 5.1 lbs).

Pulmonary Volumes

The static values for lung volumes are the following: vital capacity (VC): 4050 ± 619 ml.; residual volume (RV): 1971 ± 601 ml.; the ratio RV divided by total lung capacity (RV/TLC): $32.4 \pm 6\%$; the functional residual capacity (FRC) 2973 ± 714 ml.

Ventilation

The minute ventilation ($\dot{V}$): 9107 ± 1984.9 ml/min. The oxygen consumption ($\dot{V}O_2$): 293.7 ± 46 ml/min. The respiratory equivalent (EQ) is: 31.6 ± 7.5 .

Ventilatory Mechanics

The forced expiratory volume, one second (FEV_1) or Tiffeneau test (VEMS) is: 2797 ± 539.9 ml.; the ratio (FEV_1/VC) is: $69.3 \pm 8.0\%$; maximal voluntary ventilation (MVV) is: 106.9 ± 21.5 lit/min.

Distribution and Diffusion tests

The mean obtained value for helium mixing time is: $3' 11" \pm 48"$; the large majority of normal men did not have any signs of air trapping or Creneaux of Anthony. Some of them however did show a very slight creneau. According to our coding system the results reported in table II are 0.75 ± 0.85 for the total normal group.

The CO diffusing capacity (DL_{CO}) in normals is: 16.38 ± 4.33 ml/min/mm Hg.

REGRESSION EQUATIONS FOR NORMALS

The regression equations for some pulmonary functions tests: (VC, RV, FRC, RV/TLC, FEV_1) have been calculated. These equations are given in table III. For the sake of comparison with others, the formulae

TABLE II

COMPARATIVE TABLE OF PULMONARY FUNCTIONS BETWEEN NORMALS, CANCEROUS PATIENTS AND CHRONIC BRONCHITIC

PATIENTS, ALL ARE MEN AGED FROM 43-74 YEARS OLD

PULMONARY FUNCTION	NORMALS		LUNG CANCER		CHRONIC BRONCHITIC	
	Mean values	S.D.	Mean values	S.D.	Mean values	S.D.
VITAL CAPACITY (V.C.) in ml	4050	619.5	3129	762.9	2967	871.2
RESIDUAL VOLUME (R.V.) in ml	1971	601.8	1994	663.4	2503	790.4
RESIDUAL VOLUME/TOTAL LUNG CAPACITY (RV/TLC) in %	32.4	6.3	38.9	8.8	46.2	10.8
FUNCTIONAL RESIDUAL CAPACITY (FRC) in ml	2973	714.2	2903	796.4	3267	838.8
MINUTE VENTILATION ($\dot{V}$) ml/min.	9107	1394.9	9708	2328.3	9661	2169.7
OXYGEN CONSUMPTION ($\dot{V}O_2$) in ml/min.	293.7	46.0	285.2	54.2	278.7	52.7
FORCED EXPIRATORY VOLUME ₁ (FEV ₁) in ml	2797	539.9	1857	616.7	1498	779.3
FORCED EXPIRATORY VOLUME ₁ /VITAL CAPACITY (FEV ₁ /VC) in %	69.3	8.0	59.6	13.3	48.8	15.4
MAXIMAL VOLUNTARY VENTILATION (MVV) in L/min.	106.9	21.5	70.7	23.9	56.0	27.8
RESPIRATORY EQUIVALENT (EQ)	31.6	7.5	31.0	3.6	35.7	8.9
HELIUM DISTRIBUTION TIME (Helium Mixing time) in min. and secs.	3' 11"	48"	3' 41"	58"	4' 26"	1' 5"
CRENEAUX (Air trapping, or increase of the base line on MVV).	0.75 #	0.85 #	1.4 #	0.9 #	2.1 #	0.9 #
DIFFUSING CAPACITY _{CO} (DL _{CO}) in ml/min/mm Hg	16.68	4.3	13.5	3.9	12.3	4.3

Note: No asterisk means $p \leq 0.1$; one asterisk means $p \leq 0.05$; $\ddagger$ means $p \leq 0.01$, for the upper row of signs: this is for the comparison between that box's (Neo or bronchitics) value and Normals. The lower row (+ means $p \leq 0.01$) is for comparison between that box's (Bronchitics) values and Neos.

* Coded data for computer analysis was changed as follows: one cross = 0 to 1; two crosses = 2; three crosses = 3. evidently average values gave fractional numbers (see text for reference).

have been calculated considering sex, age in years, height in inches and weight in pounds. The standard deviations are reported for every parameter.

In order to illustrate these formulae and to compare them with others from the literature, five hypothetical pulmonary function tests of different normal subjects which differ from each other in their bodily or somatic constitution, age, height and weight have been calculated. Their values are given in table IV. The first hypothetical subject chosen is supposed to be 43 years old man weighing 132 pounds, and measuring 60 inches height. According to our formula his vital capacity (VC) is 3605 ± 620 ml. According to the formulae from Comroe, Cournand and Kory, his vital capacity is respectively: 3256 ± 870 ml; 3422 ml and 3254 ml values which are very close to ours. The same comparison can be made for the 4 other hypothetical subjects. Most values lie very closely to ours.

The regression lines for normals and their pertaining pulmonary functions related to age, height and weight have also been obtained apart the regression equations. They are shown in next chapter which deals with patients with cancer of lung and chronic bronchitis. See figures 1 through 8.

PULMONARY FUNCTIONS IN CANCEROUS PATIENTS

The pulmonary functions of 144 patients with cancer of the lung are reported. All are men in the same age group as the normals. Since the pulmonary functions of patients with cancer are compared with a group of patients with chronic bronchitis the values are given together and they are reported in table II. From there it can be seen that mean age of cancerous group is: 62.0 ± 6.7 years old; mean height is 169.0 ± 6.5 cm. (67.76 ± 2.6 inches); mean weight is: 67.1 ± 13.2 kg (147.6 ± 29.4 lbs). For chronic bronchitic patients mean age is: 61.3 ± 7.8 years old; mean height is: 169.4 ± 7.43 cms (67.8 ± 2.9 inches); mean weight: 68.9 ± 14.5 kg. or (151.5 ± 31.9 lbs).

Pulmonary Volumes

The vital capacity (VC) for cancerous patients is: 3129 ± 762.8 ml; which is significantly different from normals (4050 ± 619.5 ml) and approaches within chronic bronchitis patients' mean values of 2967 ± 871 ml. This difference is better represented by regression lines appearing in Fig. 1. From there it can be shown that there is a significant difference between those two pathologic groups of cases and normals no matter what parameters may be chosen to measure up vital capacity namely age, height or weight. It is a well known fact that vital capacity has a tendency to decrease with increasing age in adults, and to increase with height or weight (13). It is worthwhile to mention that the slopes of the curves are different between normals and the neoplastic group. The student t-test for comparison of these slopes are significantly different at 98.2% for age.

A B L E III
REGRESSION EQUATIONS OF PREDICTING FORMULAE FOR PULMONARY FUNCTIONS
GIVEN IN TABLE II

PREDICTING FORMULAE	AGE COEFF.	HEIGHT COEFF.	WEIGHT COEFF.
<u>BAUD-MORET-SCHERRER-UNDA</u>			
V.C. = $(-29 \times \text{age}) + (102.5 \times \text{h}) - 1268$	-29 ± 6.1	$102.5 \pm 18.62^*$	
R.V. = $(-2.71 \times \text{age}) + (71.5 \times \text{h}) - (0.0164 \times \text{w}) - 2194$	-2.7 ± 7.1	$71.5 \pm 25.25^*$	$0.0164 \pm 13.17^*$
F.R.C. = $(-2.32 \times \text{age}) + (108 \times \text{h}) - (0.033 \times \text{w}) - 3155$	-2.32 ± 8.2	$108 \pm 29.15^*$	$0.033 \pm 15.22^*$
RV/TLC = $(1.37 \times \text{age}) + (1.6 \times \text{h}) - (0.3 \times \text{w}) + 185$	1.37 ± 0.75	$1.6 \pm 2.67^*$	$-0.3 \pm 1.40^*$
FEV ₁ = $(-33.3 \times \text{age}) + (52.9 \times \text{h}) + 1122$	-33.3 ± 5.38	$52.9 \pm 16.45^*$	
=====			
<u>COMROE'S FROM NEEDHAM (21, 49)</u>			
V.C. = $(-38 \times \text{age}) + (121 \times \text{h}) - 2100$			
R.V. = $(26 \times \text{age}) + (110 \times \text{h}) - (11 \times \text{w}) - 4570$			
F.R.C. = $(11 \times \text{age}) + (198 \times \text{h}) - (20 \times \text{w}) - 7220$			
=====			
<u>COURMANT FROM ROSSIER (alternate of BALDWIN)</u> <u>after Comroe's and Friedberg's (3, 4, 22, 23)</u>			
V.C. = $[69.075 - (0.28 \times \text{age})] \times \text{h}$			
=====			
<u>KORY, CALLAHAN, BORKS and SYNER (43)</u>			
V.C. = $(0.052 \times \text{h}) - (0.022 \times \text{age}) - 3600$			
F.E.V. ₁ = $(0.037 \times \text{h}) - (0.028 \times \text{age}) - 1590$			

Note: The coefficients indicated by an asterisk are changed into units used throughout this study, i.e.:
h = height in inches; w = weight in pounds.

TABLE IV
COMPARATIVE VALUES FOR FIVE NORMAL HYPOTHETICAL MEN ACCORDING TO PREDICTING FORMULAE

PULMONARY FUNCTIONS Regression Equations are those from Table III	SOMATIC CONSTITUTION									
	AGE in years :		43		43		53		63	
	HEIGHT in inches:		60		72		74		64	
	HEIGHT in pounds:		132		176		209		154	
	S.D.		S.D.		S.D.		S.D.		S.D.	
<u>BAUD-MORET-SCHERER-UNDA</u>										
V.C. in ml	3605	620	4829	620	4734	620	3404	620	2706	620
R.V. in ml	1977	587	2840	587	2956	587	2214	587	1898	587
F.R.C. in ml	3226	679	4515	679	4707	679	3605	679	3148	679
RV/TLC in ml	30.0	6.2	30.6	6.2	31.3	6.2	32.8	6.2	34.3	6.2
F.E.V. ₁ in ml	2864	448.6	3499	448.6	3272	448.6	2410	448.6	1831	448.6
<u>COMROE'S FROM NEEDHAM (21, 49)</u>										
V.C. in ml	3256	970	4978	970	4840	970	3250	970	2348	970
R.V. in ml	1696	900	2532	900	2649	900	2414	900	2502	900
F.R.C. in ml	2493	1300	3989	1300	3835	1300	3065	1300	2834	1300
<u>COURMARD FROM ROSSIER (alternate of BALDWIN) after Comroe's and Friedberg's (3, 4, 22, 23)</u>										
V.C. in ml	3422		4107		4013		3292		2901	
<u>KORY, CALLAHAN, BOREN and SYNER (43)</u>										
V.C. in ml	3254	650	4814	962	4854	970	3334	667	2572	514
F.E.V. ₁ in ml	1585	317	1584	316	1584.6	316	1585.8	317	1586.5	317

* This S.D. is calculated from its corresponding value as $20\% \pm$

The residual volume is: 1994 ± 663.4 ml in the cancerous patients which is not statistically different from normals (1971 ± 601.8) but the mean value for chronic bronchitic 2503 ± 790.4 ml is significantly different from both, normal and neoplastic patients. The differences are more apparent in Fig. 2 where the regression lines for normal and cancerous patients are very intertwined one to another, but they are not close to the mean values of chronic bronchitic patients. It should be pointed out that from Fig. 2 it appears that age and weight bear no relationship whatsoever to residual volume according to the correlation coefficient value with all reserves mentioned in description of statistical analysis. Whereas increasing height is definitely related to an increase of residual volume.

The mean values for the ratio residual volume over total lung capacity (RV/TLC) in cancerous patients is: $38.9 \pm 8.8\%$. That is significantly different than the mean values for chronic bronchitics ($46.2 \pm 10.8\%$). The mean values of normal subjects ($32.4 \pm 6.3\%$) is significantly different than both pathological groups. Fig. 3 shows the regression lines for all three groups. From there it can be seen that in normals there is no relationship for this ratio with age, height or weight. Whereas there is a very marked tendency for this quotient to increase with increasing age and decrease with increasing weight in chronic bronchitic patients. The slopes of the curves of regression lines are apparently different in the 3 groups of subjects however that they are not statistically significant according to t-tests between neoplastic and bronchitics, because the lines are almost parallels. Anyway the slopes are steeper in bronchitic patients especially when considering age and weight. In function of height the ratio (RV/TLC) is not significant at all.

For the functional residual capacity the mean values for cancerous patients is: 2903 ± 796.4 ml; this value is not different from normals (2973 ± 714.2 ml). However it is different from chronic bronchitic patients whose mean is 3267 ± 838.8 ml and this latter with reference to normals.

Ventilation

The minute ventilation ($\dot{V}$) mean value is: 9708 ± 2328 ml in cancerous group whereas chronic bronchitics have a mean value of 9661 ± 2169 ml/min. The increase is significant between chronic bronchitics and normals (9107 ± 1984.9 ml/min.). The difference between cancerous and bronchitics is insignificant. The mean value for respiratory equivalent (EQ) is: 35 ± 8.6 in cancerous patients and 35.7 ± 8.9 in chronic bronchitic patients. The difference with regards to normals (31.6 ± 7.5) is slight but is nevertheless statistically significant when considering the t-test ($p = 0.01$).

Lung Mechanics

The one second forced expiratory volume (FEV_1) in cancerous patients is 1857 ± 616.7 ml; and in chronic bronchitic patients is: 1489 ± 779.3 ml;

VITAL CAPACITY

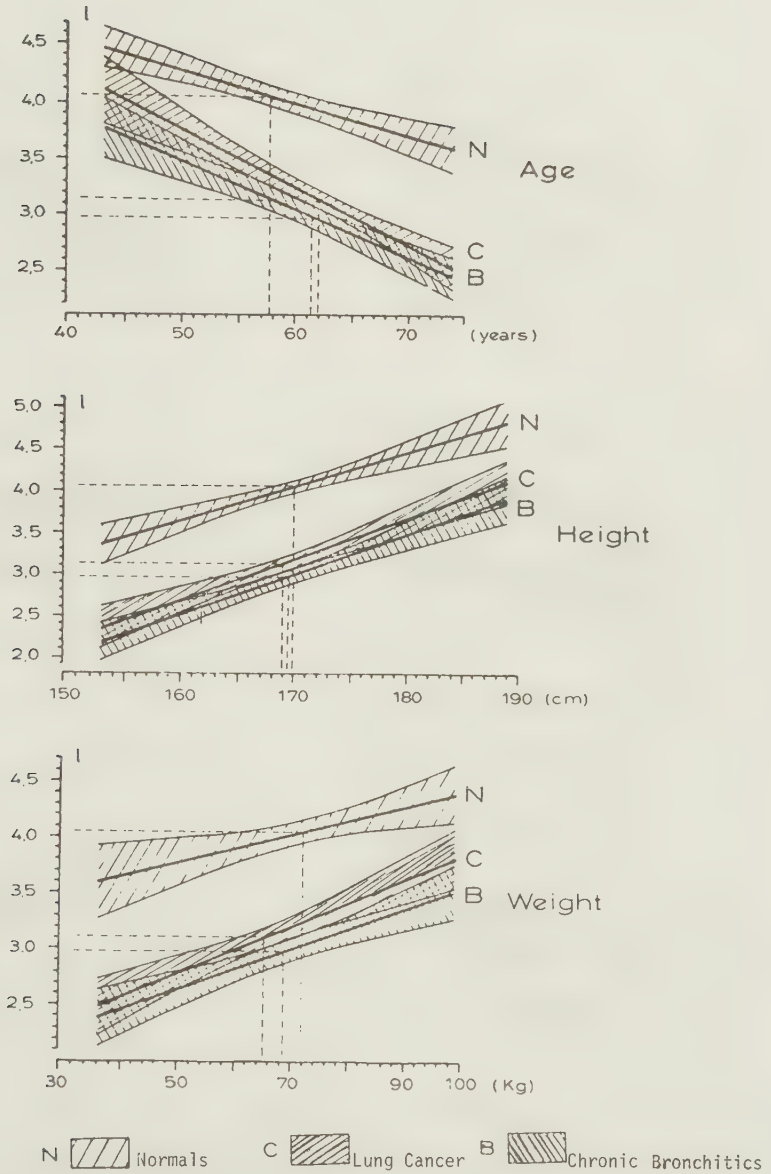
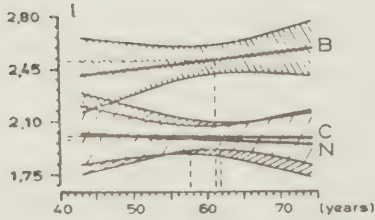
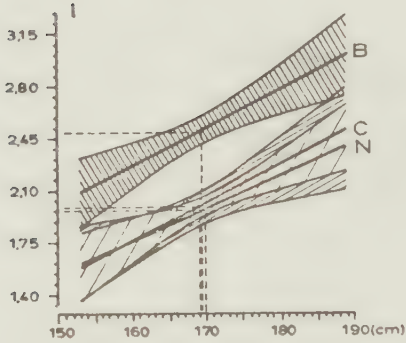


FIG.1: Regression lines for Vital Capacity (VC) on age, height and weight for the three populations of cases studied: normals, neoplastic and chronic bronchitics. Notice: height is in cms, and weight in Kilos as given in our original files.

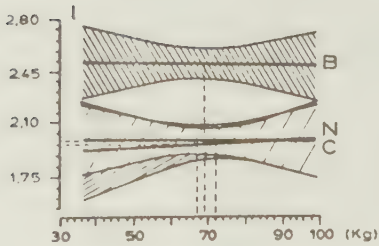
Residual Volume



AGE



Height



Weight

N Normals

C Lung Cancer

B Chronic Bronchitics

FIG. 2: Regression lines for the Residual Volume on age, height (in cms.) and weight (in Kg.).

RV/TLC

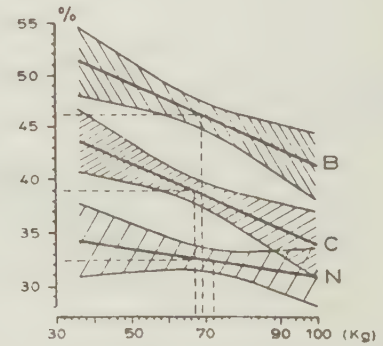
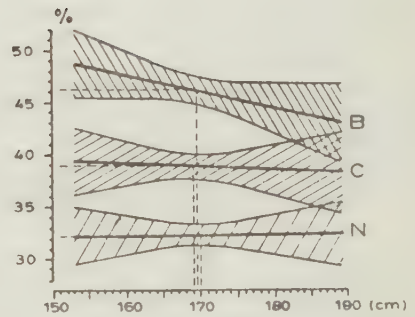
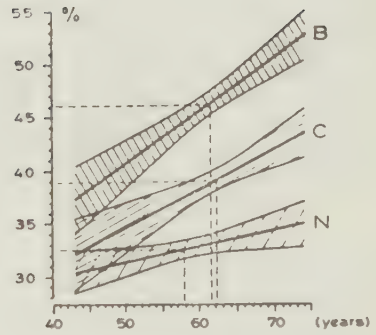
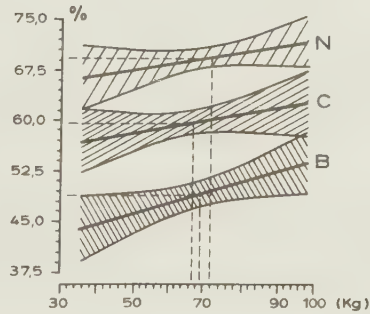
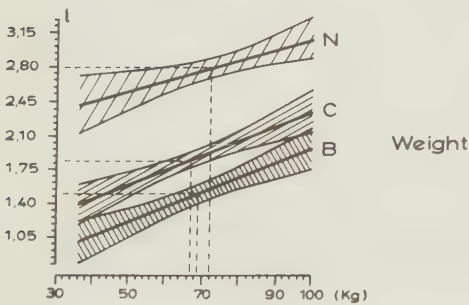
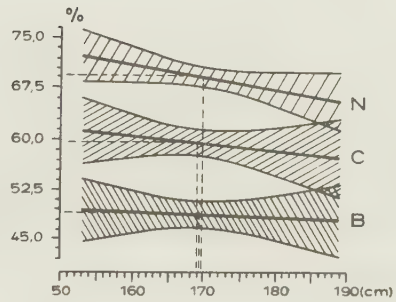
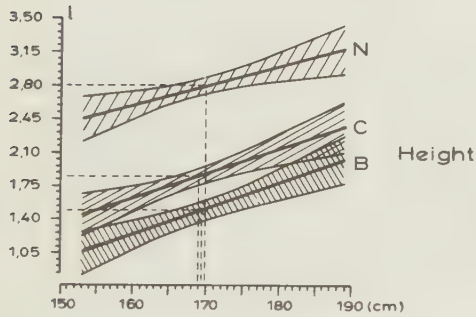
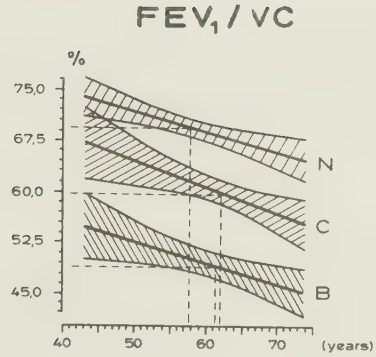
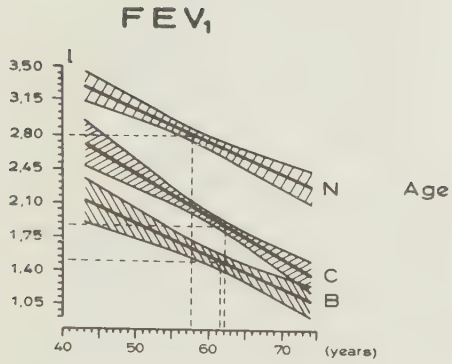


FIG. 3: Regression lines for the ratio (RV/TLC) on age, height (in cms.) and weight (in Kg.).



N Normals

C Lung Cancer

B Chronic Bronchitics

FIG. 4: Regression lines for the one second Forced Expiratory Volume on age height (in cms.) and weight (in Kg.) for the three groups of subjects.

FIG. 5: regression lines for the ratio (FEV₁/VC) on age, height (in cms.) and weight (in Kg.).

these ciphers are significantly different from normals (2797 ± 539.9 ml). In cancerous patients mean values are situated midway between those of normals and those of chronic bronchitics, their values being the lowest. Regression lines of Fig. 4, show a decreasing tendency of FEV_1 related to age in normals and in neoplastic patients. Whereas FEV_1 values have an increasing tendency related to increasing height and weight.

The one second forced expiratory volume, divided by vital capacity (FEV_1/VC) is $59.6 \pm 13.3\%$ in cancerous patients and $48.8\% \pm 15.4\%$ in chronic bronchitic patients. Normal values are: $69.3 \pm 8.0\%$. The significant difference is evident among all these groups. Regression lines in Fig. 5, shows a slight diminishing tendency in all three groups to decrease when related to age (statistically significant) and height whereas it seems slightly increasing with increasing weight. Although for height and weight are statistically not significant.

The mean value for the maximal voluntary ventilation (MVV) in the cancerous group is: 70.7 ± 23.9 lit/min.; whereas that of chronic bronchitics is 56 ± 27.8 lit/min. The differences are quite significant with reference to normals (106.9 ± 21.5 lit/min.) and from the bronchitic group to the neoplastic group. Regression lines in Fig. 6 shows a marked difference between normals and the 2 pathologic groups for the parameters considered. The steepness of the curve for cancerous patients is more pronounced than the curve for chronic bronchitic patients. The t-test for comparison of slopes is significant at 96.1%.

Distribution and Diffusion tests

The helium distribution time (He-t) mean values is: $3' 41'' \pm 58''$ in cancerous patients and $4' 26'' \pm 1' 5''$ in bronchitic patients which is significantly different from normals ($3' 11'' \pm 48''$). Regression lines in Fig. 7 shows a slight increasing tendency to increase with age for normals and neoplastic. This is more evident for bronchitics. However, there is no relationship at all with height; there is a slight decreasing tendency with weight for neoplastic and bronchitic patients.

As far as the creneaux of Anthony are concerned they were of moderate amplitude for cancerous patients. According to our coding system mean value is: 1.4 ± 0.9 (Normal 0.75 ± 0.85). For the chronic bronchitic patients the creneaux were of important amplitude, mean value is 2.1 ± 0.9 .

The diffusing capacity (DL_{CO}) mean value for cancerous patients is: 13.5 ± 3.9 ml/min/mm Hg and 12.3 ± 4.3 ml/min/mm Hg for chronic bronchitics, that of normals is 16.4 ± 4.33 ml/min/mm Hg. There is a statistically significant difference between normals and the two pathologic groups on one side, and between cancerous and bronchitics on the other side. Regression lines in Fig. 8 shows DL_{CO} having a decreasing tendency with increasing age, and increasing tendency with increasing height and weight; the steepness of the curves are equally pronounced in cancerous patients and in normals when considering the weight. The t-tests for comparison of slopes are statistically not significant.

MAXIMAL VOLUNTARY VENTILATION

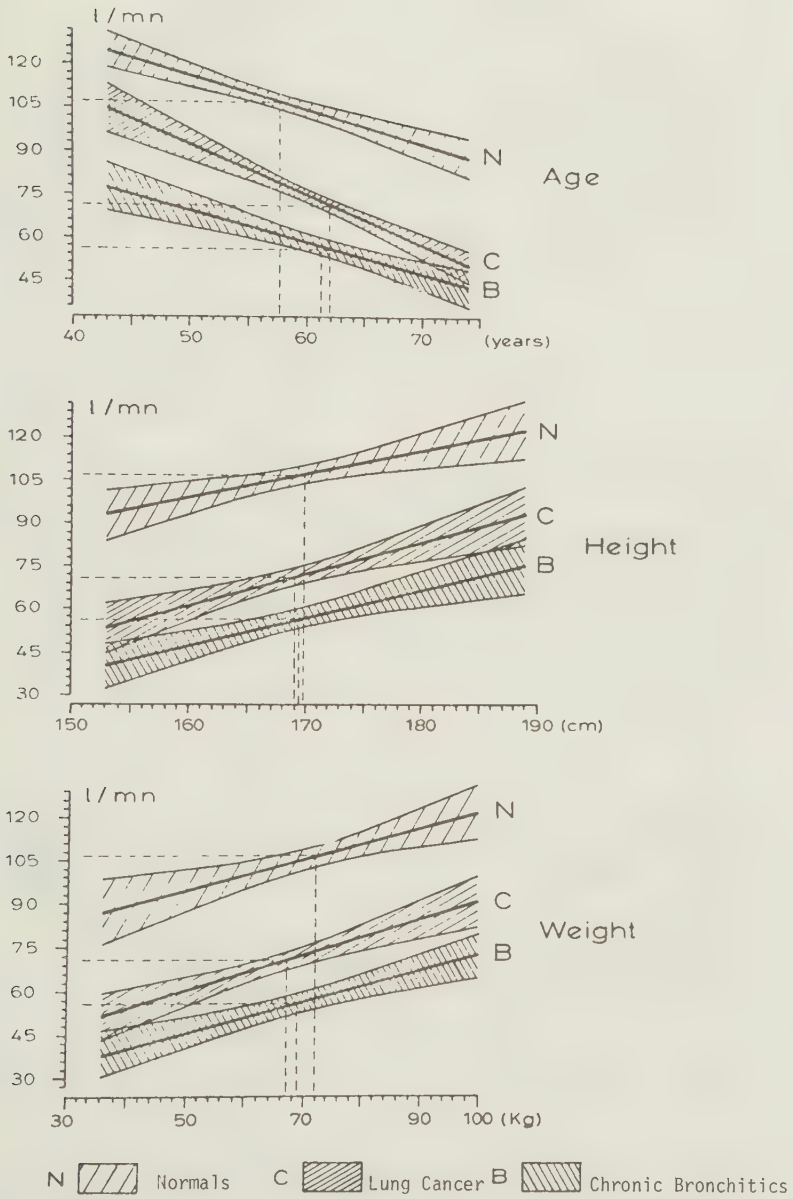
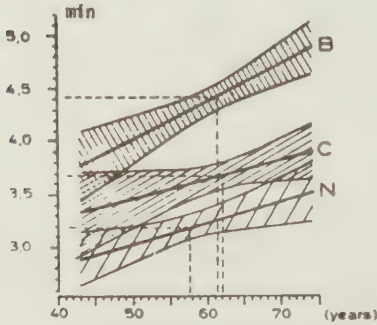
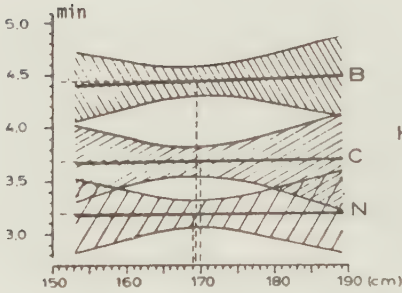
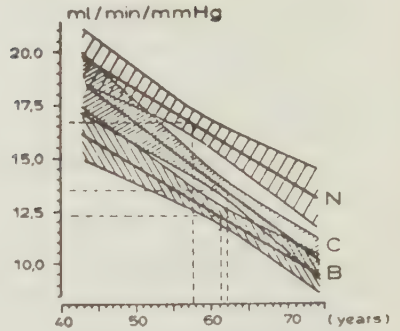


FIG. 6: Regression lines for the MVV on age, height (in cms.) and weight (in Kg.).

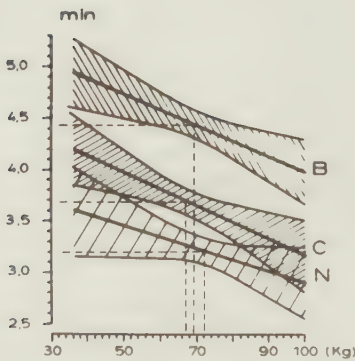
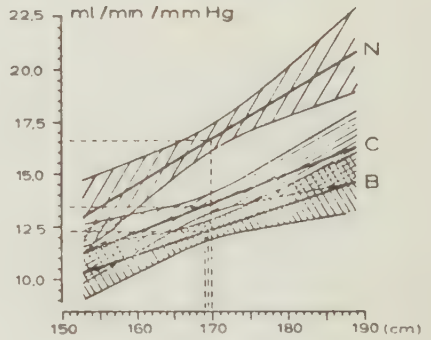
HE DISTRIBUTION TIME



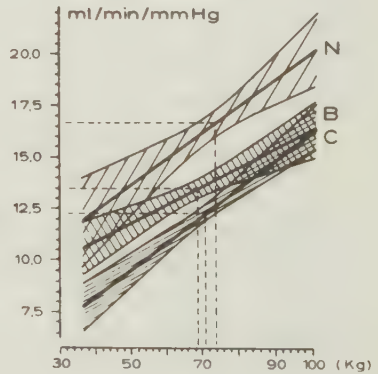
DIFFUSING CAPACITY



Height



Weight



N Normals

C Lung Cancer

B Chronic Bronchitics

Fig. 7: Regression plots for helium distribution time on age, height (in cms.) and weight (in Kg.).

Fig. 8: Regression lines for the diffusing capacity (DL_{CO}) for all three groups on age, height (in cms.) and weight (in Kg.).

DISCUSSION

MATERIALS AND METHODS

Selection of normal men in this study represents a choice made among hospitalised subjects who did not show any cardiovascular or cardiopulmonary affection. Actually they are not normal subjects "sensu strictu" chosen as such from a global normal population of healthy individuals. Nevertheless they are considered as normal because they are neither affected by cardiopulmonary disease nor any other disease that might have impinged upon pulmonary performance. 76% of those cases were smokers. This might be an explanation of some of their complaints of dyspnoea at effort, coughing and expectoration. It has been reported that pulmonary functions diminish in normal young smokers (25, 32, 34, 37, 59, 60) with increasing quantity and quality of sputum, but we have not attempted to differentiate pulmonary functions between smokers and no-smokers in normal men.

Patients with lung cancer represent equally a certain choice. We have considered in this paper only those operable cancerous patients. They were patients presenting a well localised pulmonary lesion (1, 35) without important visible metastasis or atelectasis on X-rays, which might have contraindicated by themselves a surgical intervention. All other cases were discarded from our study. A fact worth mentioning is that the majority of cancerous patients had their pulmonary functions tested (105 out of 144) one month after their beginning symptoms appeared. Whereas for chronic bronchitic patients their pulmonary functions were measured several months and even years after their symptomatology first appeared.

All patients sent to the Pulmonary Functions Laboratory with a clinical history of chronic bronchitis are considered for this work. This represents a sampling population of the particular disease far more complete than the normal group and the group with lung cancer actually hospitalised in the internal medical service.

The smokers percentage in all groups is fairly high: 76% for normals, 93% for lung cancer patients, and 87% for chronic bronchitis. Clinical symptoms such as coughing, dyspnoea and expectoration vary widely from one group to another. One quarter of the normal subjects presented light exertional dyspnoea symptoms coughing and/or expectoration most probably due to smoking habits. In cancerous patients dyspnoea coughing and expectoration were clearly more pronounced than in normals (14, 16, 25, 59, 60). In chronic bronchitic patients these symptoms were even more accentuated than in cancerous patients and evidently more than in normal cases (4, 9, 21, 66). The difference in these symptomatology seems not to come from smoking itself in the two pathologic groups but from their basic illness.

The methods used to measure pulmonary functions are the classical ones described (1, 5-7, 10, 13, 19, 21-23, 29, 34, 43, 45, 56-58, 62). We have combined the tests for distribution and diffusion of gases. The difficulty of distinguishing the troubles of distribution from those of diffusion of gases is well known since in most cases one goes hand in hand with the other (53, 54, 65, 66). It is actually controversial that troubles of diffusion tested by DL_{CO} methods do not in fact represent diffusion troubles alone but may be falsified by distribution disturbances. A rather recent observation made by Fraimow et al. (30) is of particular interest because it shows that under certain circumstances the DL_{CO} test may be useful to indicate diffusion disturbances. He observed a fall, after 2 hours of Ethiodol injection for Lymphography tests, of DL_{CO} without altering the other pulmonary function tests including the distribution tests. Since pulmonary oil emboli resulted invariably, it is highly probable that the diminution of DL_{CO} test in this specific condition was the consequence of decreased permeability of the alveolo-capillary membrane. A further point stressing the reliability of DL_{CO} is given by measuring it in anemic patients without pulmonary disease (having normal pulmonary functions -except DL_{CO} -) and without uneven distribution (53) and showed improved DL_{CO} after blood transfusions. There exist also clinical conditions (pneumoconiosis, interstitial pneumonia, etc.) (2, 10, 21, 24, 26) in which the distribution troubles are absent but the only functional modification being a diminution of DL_{CO} (27, 28, 44, 48, 57, 69). However care should be given when interpreting this parameter in cancerous patients, since rigid conclusions concerning diffusion troubles should be avoided.

PULMONARY FUNCTIONS IN NORMALS

In normals the pulmonary functions measured are much alike those reported by other authors considering the parameters sex, age, height and weight. The calculated regression equations to predict their pulmonary functions according to these same parameters are quite similar. The regression lines obtained by computer plots serve perfectly well to compare all mean values and its distribution from one group to another. The accuracy of our predicting equations for some of the pulmonary functions are checked against predicting formulae and obtainable values given in the literature (3, 4, 10, 13, 19, 21, 23, 31, 43, 49, 67, 68). The validity of our normals' values were equated by choosing 5 hypothetical subjects' pulmonary functions: their values fitted perfectly well all predicting equations from our resort and all predicting equations reported by Comroe's from Needham (21, 49) Cournand from Rossier (22, 23) Kory et al. (43, 63). The regression coefficients of our formulae, certainly do intercept the coefficients from those given in the literature. It is highly relevant to observe at first glance that our values are very close to those obtained by calculating with regression formulae given in the mentioned references. This necessarily

means that our limits of error are situated within the limits of error given by others' formulae. Therefore our values are not or can not be significantly different from theirs despite the fact that our normal cases are not a random sampling from a healthy population, and furthermore they were hospitalised subjects without cardiovascular or pulmonary impairment. These statistical comparisons let us believe that our normal values for men established in our laboratory are within standard techniques of quantification much alike those given by the literature.

It is well known that vital capacity (VC), residual volume (RV), maximal voluntary ventilation (MVV), the one second forced expiratory volume (FEV_1), the helium distribution time and diffusing capacity (DL_{CO}), vary according to age, height and weight. This fact was confirmed in our study considering the same parameters to equate existing relationships. In terms of survival rates (13, 21, 68) the regression line of vital capacity on age is very significant in all three groups. The slope of the line being steeper for lung cancer patients it seems evident that their lifespan is shortened.

We have not attempted in this work to define which of the three parameters, age, height or weight fitted best the correlation for every one of the different pulmonary functions. It is worth mentioning that the residual volume in our study has not shown an increasing tendency with age. This may be so apparently since, as we have already mentioned, we have not statistically tested for the straightness of the line for this variable. Furthermore these values are for a given age range. Knowing on the other hand that residual volume is related to functional residual capacity (FRC) and total lung capacity (TLC) it is evident that their regression lines do actually show an increasing tendency on age.

PULMONARY FUNCTIONS IN PATIENTS WITH CANCER OF THE LUNG

The study of 144 patients with a fairly well localised operable cancerous lesion has shown, by their pulmonary functions that there exists in these patients -on the absence of important clinical history of chronic bronchitis- a very clear cut functional pulmonary deficit. This deficit is characterised by an important diminution of the vital capacity (VC), forced expiratory volume, one second, (FEV_1), the ratio FEV_1/VC , maximal voluntary ventilation (MVV) and the diffusing capacity (DL_{CO}). Concomittantly, there is a significant increase of residual volume divided by total lung capacity (RV/TLC), the helium distribution time, the Respiratory Equivalent and the minute ventilation ($\dot{V}$). It is also noticeable the presence of Creneaux of moderate amplitude were apparent on the spirographic recording, as well as some signs of air trapping. Nevertheless and surprisingly enough the residual volume (RV) and the functional residual capacity (FRC) were not increased on the average when compared to normals' average values. A slight restrictive

syndrome in lung cancer patients can be also recognized by the decreased VC and DL_{CO} , by a slight increase in $\dot{V}$ without increase of $\dot{V}_{O_2}$. The fact that the ratio RV/TLC is statistically significantly increased without increase in RV indicates that there exists a decreased TLC. This makes part of a restrictive syndrome (21). The same observations are reported by other investigators according to the extent to which the pulmonary cancer has impinged upon pulmonary functions (1, 3, 5, 10, 17, 28, 35, 40, 42, 44, 50, 51).

It is generally agreed that in most cases with lung cancer their pulmonary functions reveal an obstructive syndrome (14, 52, 54, 64, 65, 70, 73). Especially in advanced cases of lung cancer the pulmonary functions most severely decreased are the FEV_1 and the MVV together with troubles of distribution and diffusion of gases. In Jesek's paper (38, 39) VC, FEV_1 , and MVV were diminished in the same proportion as our group of cancerous patients, however he did not notice a changement in the ratio FEV_1/VC and furthermore he had in his preoperative lung cancer patients a much higher increase of RV and of the ratio RV/TLC. The same observations are reported by other authors using other pulmonary function techniques (2, 57, 73). Everything occurs then in cancerous patients as if there would be an obstructive syndrome without the presence of a true obstruction. The pattern of obstruction is better represented by the chronic bronchitic patients whose pulmonary deficit is greater. In these patients there is a diminution of FEV_1 , MVV, FEV_1/VC . There exist an increase of helium distribution time, functional residual capacity (FRC), residual volume (RV) and of the ratio residual volume divided by total lung capacity (RV/TLC). In clinical practice these findings go hand in hand with auscultatory signs of factual obstruction. Other findings from the spirographic recording include important signs of Air trapping and Creneaux of Anthony. Most emphysematous and some asthmatic patients have similar pulmonary dysfunction traducing pulmonary hyperinflation (4, 6, 7, 9, 10, 12a, 16, 55).

In cancerous patients neither the true signs of obstruction have been found nor those of hyperinflation. There are however disturbances of distribution and diffusion of gases as shown by average values of DL_{CO} . On the whole these values are a little less marked than in the chronic bronchitic patients. In both pathological groups the vital capacity is decreased in an identical manner the reasons being probably different: in cancerous patients vital capacity is decreased due to the functional loss of pulmonary tissue or by engorgement of lymphatic tissue and interstitial space by cancerous cells. In chronic bronchitis vital capacity is diminished mainly due to alterations of pulmonary parenchyma and by an increase of functional residual capacity or residual volume. The functional differences among cancerous and bronchitic patients are equally corroborated upon clinical grounds. Dyspnoea, coughing and expectorations go hand in hand with auscultatory signs of air turbulence and wheezing which are all signs of bronchial obstruction.

These are far more evident and accentuated in bronchitic than in cancerous patients in whom (despite mean obtained values of significant dyspnoea coughing and expectorations) few or no auscultatory disturbances may be observed (10, 21, 23, 68).

Altogether pulmonary functions in cancerous patients present ventilatory and diffusion troubles. Emirgil et al. (28), Balvanera et al. (5) have shown with anatomoclinical confrontation in cancerous patients that pulmonary functions differ slightly according to lymphogenic spread metastasis to lung or blood spreading metastasis. In both cases the DL_{CO} was very significantly decreased but it was far more diminished in those with lymphogenic metastasis. They also demonstrate the presence of venous arterial shunt-like mechanisms (5, 26, 28, 50, 57, 64). These anatomoclinical confrontations evidence ventilation-perfusion troubles in cancerous patients. All cases presented an obstructive syndrome with a slight accompanying restrictive syndrome.

Concerning smoking habits of cancerous patients we must emphasize that studies carried out in young normal smokers have demonstrated that cigarette consumption alters pulmonary functions significantly especially FEV_1 and MVV (14, 37, 46, 59). Quantity and quality of sputum is worsened at the same rate. Our cancerous patients being smokers by a large majority may have, by this reason alone, altered to a certain extent their pulmonary performance. A recent study has shown that cigarette smoking perturbs the DL_{CO} and all its components (25, 32).

The main interest of investigators has been centered around the usefulness of pulmonary functions in order to assess operability, the anesthetics risks and as a post-operative prognostic value (15, 16, 18, 28, 33, 35, 38, 39, 40, 42, 44, 47, 48, 51, 52, 58, 61) Ugglä (72) has shown that only VC and MVV are of prognostic value when confronted to resting pulmonary artery pressure without occlusion, whereas by occluding the pulmonary artery only the arterial oxygen tension and saturation were of prognostic value in patients with various diseases including some cases of lung cancer. Jornod et al. (41) reporting 6 cases of severe pulmonary hypertension (49) found the DL_{CO} diminished when all pulmonary functions were roughly normal. The DL_{CO} measurement was the best pulmonary function test to be used as a guide for long term prognosis in their pulmonary hypertension cases.

The DL_{CO} measurements in patients with lung cancer is perhaps quite useful as a prognostic value and to foresee operability risks. Besides it may inform us about the true extent of the tumor invasion by lymphatic engorgement which are most often not revealed by the radiologic image. Further studies are necessary for a careful interpretation and a correct usage of the pulmonary functions in the clinical assessment of patients with cancer of the lung.

CONCLUSIONS

The pulmonary functions have been measured in a group of 104 normal male hospitalised subjects without cardiovascular or pulmonary impairment and their values were identical to other investigators values, as verified by their and our predicting formulae for a given age, sex, height and weight.

In a group of 144 males with lung cancer an obstructive syndrome without actual obstruction was found, as shown by the diminution of vital capacity (VC), the one second forced expiratory volume (FEV_1) the maximal voluntary ventilation (MVV) and no increase of residual volume (RV) was noted but a slight increase of the ratio (RV/TLC). However a significant decrease of diffusing capacity (DL_{CO}) together with some signs of distribution-disturbances of gases was observed.

In order to emphasize the similarities and differences of the obstructive syndrome found in cancerous patients, the pulmonary functions were compared with a group of 172 men having chronic bronchitis who presented a real obstructive syndrome with actually increased residual volume (RV) functional residual capacity (FRC) and the ratio (RV/TLC) with a diminution of DL_{CO} identical or even more accentuated than in the cancerous patients.

The three groups of subjects have been compared by means of regression lines drawn and its pertaining envelopes of confidence limits. All calculations have been done by computer analysis.

Special attention has been given to diffusing capacity (DL_{CO}) since according to other investigators it seems that a diminution of DL_{CO} seems to be related to anatomic invasion of tumor in lymphatic or blood vessels.

The diminution of pulmonary functions as obtained by our results in lung cancer patients were rather surprising especially when confronted with clinical findings and radiologic images. These findings stress the importance of investigating the pulmonary functions in cancerous patients especially to determine: 1) the degree of functional impairment 2) to estimate the pre-operative risks; 3) to foresee the final outcome of lung resected patients and 4) to establish a long term prognosis.

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